VERSION TO SHOW MARKED CHANGES IN SPECIFICATION

Please substitute the following replacement paragraph for the paragraph bridging page 4, line 25 through page 5, line 6 of the above-identified application:

The intrabody comprises whole antibodies, heavy chains, Fab' fragments, single-chain antibodies and diabodies. In one preferred method of the present invention, the intrabody comprises a single-chain antibody (sFv). If the target is a receptor, the antibody contains a leader sequence and an ER or Golgi appropriate retention signal, such as KDEL (SEQ ID NO: 17). Preferably, cells are transduced with a single-chain antibody to human MHC-1 (sFvMHC-1) containing a leader sequence and an endoplasmic reticulum (ER) such as, e.g., a KDEL sequence or golgi apparatus retention signal. Such a method prevents expression of the MHC-1 molecules on the surface of cells. The downregulation of MHC-1 molecules is useful for controlling particular immune responses, such as tissue rejection, autoimmune diseases and bone marrow transplantation. In another embodiment, the target would be elsewhere in the cell and a functional leader sequence would not be present.

Please substitute the following replacement paragraph for the paragraph bridging page 14, lines 16-31 of the above-identified application:

In many cases, it is desirable to knock out the antigen itself, before it binds the IRM, e.g., MHC-1 molecules, to prevent presentation on the cell surface. In such a case, intrabodies to the antigen, be it a peptide, or its degradation product, can be used to selectively prevent the binding of antigen to the IRM. The intrabody can be targeted to the different cellular compartments, by using the appropriate leader sequence, to intercept the antigen at various points along the antigen presentation pathway. For example, SIINFEKL (SEQ ID NO: 56) is a known cellular degradation product of ovalbumin. It is known that introduction of ovalbumin into the cytosol leads to its proteolytic processing and presentation on MCH-1 molecules. Moore et al., *Cell*, Vol. 54, 777-785 (1988); Rock, et al., *Cell*, Vol. 78, 761-771 (1994). An antigen such as albumin could be targeted in the cytosol before degradation by the proteasome. After degradation, one could target the degradation product, e.g., SIINFEKL, (SEQ ID NO: 56) prior

to binding with TAP, or in the ER, prior to binding the MHC-1 molecule. The binding of the intrabody to the antigen prevents presentation of the antigen on the cell surface.

Please substitute the following replacement paragraph for the paragraph bridging page 15, line 28 through page 16, line 9 of the above-identified application:

The antibodies for use in the present invention can be obtained by methods known in the art against the IRM or antigen of interest. For example, single chain antibodies are prepared according to the teaching of PCT/US93/06735, filed on January 17, 1992 and U.S. Patent Application No. 08/350,215, filed on December 6, 1994, incorporated herein by reference. In one embodiment, the antibody is constructed so that it is directed to and remains in the lumen of the ER of the target cell. Such construction can be readily achieved by known methods so that the intrabody contains an ER-retention signal, e.g., KDEL (SEQ ID NO: 17). An example setting forth the construction of an ER-expressed intrabody to MHC-1 molecules using ATCC HB94 hybridoma cells (fusion name BB7.7, anti-HLA-A,B,C) is set forth below. Based on this teaching and the known art, intrabodies, e.g., sFvs, to other IRMs can readily be obtained by the skilled artisan.

Please substitute the following replacement paragraph for the paragraph bridging page 22, line 14-23 of the above-identified application:

Alternatively, one can use a known antibody to the target protein. Thereafter, a gene to at least the antigen binding portion of the antibody is synthesized as described below. As described briefly above, in some preferred embodiments it will also encode an intracellular localization sequence such as one for the endoplasmic reticulum, nucleus, nucleolar, etc. When expression in the ER normal antibody secretory system such as the endoplasmic reticulum-golgi apparatus is desired, a leader sequence should be used. To retain such antibodies at a specific place, a localization sequence such as the KDEL (SEQ ID NO: 17) sequence (ER retention signal) may be used. In some embodiments the antibody gene preferably also does not encode functional secretory sequences.

Please substitute the following replacement paragraph for the paragraph bridging page 25, line 28 through page 26, line 6 of the above-identified application:

To prepare anti-MHC-1 sFvs one could use the primer sequences A(SEQ ID NO:49) and B(SEQ ID NO:50) for V_H, C(SEQ ID NO:51) and D(SEQ ID NO:52) for V_L, which are set forth in Table 3. A preferred interchain linker for this antibody would be $(gly\text{-}gly\text{-}gly\text{-}gly\text{-}ser)_3$ (SEQ ID NO: 1) and can readily be prepared by peptide synthesizers or excised and amplified by PCR from a plasmic containing this sequence. The sFv can be assembled from the various fragment (V_H, V_L, and interchain linker) by overlap extension [Horton, R.M., et al. *Gene 77*:61-68 (1989)] followed by amplification with primers SEQ ID NO:49 and SEQ ID NO:52. The complete sequence can be confirmed by the dideoxy chain termination method of Sanger [*Proc. Natl. Acad. Sci. USA 74*:5463-5467 (1977)].

Please substitute the following replacement paragraph for the paragraph bridging page 30, line 17 through page 31, line 10 of the above-identified application:

In theory, there are multiple points within the secretory pathway at which an intrabody can be placed to bind and divert a trafficking protein from its ultimate destination. The ER is a preferred location because it permits trapping proteins early in their biosynthesis and creates potential for the rapid disposal of immune complexes by degradative systems within the ER [Klausner, R.D. & Sitia, R., *Cell* 62:611-614 (1990)]. Peptide signals required for the ER-retention of soluble proteins are well characterized and the carboxy terminal tetrapeptide Lys-Asp-Glu-Leu (KDEL) (SEQ ID NO: 17) [Munroe, S. & Pehham, H.B., *Cell* 48:899-907 (1987)] is a preferred sequence. The efficiency of the ER retention system is in part due to the existence of a retrieval mechanism which returns KDEL-tagged (SEQ ID NO: 17) proteins to the ER if and when they escape into the *cis* golgi network [Rothman, J.E. & Orci, L., *Nature* 355:409-415 (1992)]. The ER is also the natural site of antibody assembly as it is the residence to molecular chaperones such as BiP and GRP94, which assist in the correct folding of immunoglobulin molecules [Melnick, J., et al., *Nature* 370:373-375 (1994)]. The ER also offers the advantage that ER-resident proteins often show extended half-lives.

Please substitute the following replacement paragraph for the paragraph on page 31, lines 19-25 of the above-identified application:

The intrabodies bind to and form a complex with the molecules of interest intracellularly. By use of appropriate targeting signals, for example, the endoplasmic reticulum retention signal, such as KDEL, (SEQ ID NO: 17) one can further tailor the intrabodies. For example, one can prepare antibodies for MHC-1 (1) without any targeting signal (sFvMHC) and (2) with an endoplasmic reticulum retention signal (KDEL) (SEQ ID NO: 17) (sFvMHCKDEL). Genes encoding these sFvs can then intracellularly inserted into mammalian cells.

Please substitute the following replacement paragraph for the paragraph on page 38, lines 18-23 of the above-identified application:

We isolated two specific Vkappa chains and so we had two series of sFvs, labeled as anti-MHC-1-5k and anti-MHC-1-8k sFvs, representing two different anti-MHC-sFvs with similar heavy chain and different kappa chains. Both had a C-terminal SEKDEL (SEQ ID NO: 13) sequence specific for ER-retention. The nucleotide and amino-acid primary sequence is shown in Figures 2A and 2B (sFvhMHC-1-5k) and Figures 2C and 2D (sFvhMHC-1-8k).